

Original Article

Open Access



Genetic study of the *NUS1* gene variants in Han Chinese patients with Parkinson's disease

Cui Gao^{1,2,#}, Lamei Yuan^{1,2,3,#}, Wen Zheng⁴, Yan Yang⁴, Zhi Song⁴, Yi Guo⁵, Hao Deng^{1,2,3,4,*}

¹Research Center of Medical Experimental Technology, the Third Xiangya Hospital, Central South University, Changsha 410013, Hunan, China.

²Center for Experimental Medicine, the Third Xiangya Hospital, Central South University, Changsha 410013, Hunan, China.

³Disease Genome Research Center, Central South University, Changsha 410013, Hunan, China.

⁴Department of Neurology, the Third Xiangya Hospital, Central South University, Changsha 410013, Hunan, China.

⁵Department of Medical Information, School of Life Sciences, Central South University, Changsha 410013, Hunan, China.

#Authors contributed equally.

Correspondence to: Prof. Hao Deng, Research Center of Medical Experimental Technology, the Third Xiangya Hospital, Central South University, 138 Tongzipo Road, Changsha 410013, Hunan, China. Email: hdeng008@163.com

How to cite this article: Gao C, Yuan L, Zheng W, Yang Y, Song Z, Guo Y, Deng H. Genetic study of the *NUS1* gene variants in Han Chinese patients with Parkinson's disease. *Ageing Neur Dis.* 2025;5:9. <https://dx.doi.org/10.20517/and.2024.36>

Received: 14 Nov 2024 **First Decision:** 14 Dec 2024 **Revised:** 3 Mar 2025 **Accepted:** 21 Apr 2025 **Published:** 28 Apr 2025

Academic Editors: Xiaojiang Li, Can Zhang **Copy Editor:** Xing-Yue Zhang **Production Editor:** Xing-Yue Zhang

Abstract

Aim: Parkinson's disease (PD) is the second most common progressive neurodegenerative disease linked to genetic and other factors. The *NUS1* dehydrolipoyl synthase subunit gene (*NUS1*) variants were reported to be associated with PD. In this PD-control cohort, we aimed to explore the potential role of the *NUS1* gene variants in PD.

Methods: A cohort of 512 Han Chinese sporadic PD patients and 516 ethnically and age-matched controls underwent clinical evaluation. Peripheral blood samples were then collected, and whole-exome sequencing was performed. The potential PD-related variants identified through screening were verified using Sanger sequencing, further classified, and subsequently analyzed by bioinformatics analysis tools. Statistical analysis was conducted to assess the association between the variants and PD.

Results: Three *NUS1* heterozygous missense variants, including c.127G>T (p.Ala43Ser, rs1327892878), c.487G>C (p.Asp163His, rs369403261), and c.537T>A (p.Asp179Glu, rs28362519), were identified. Two rare variants, c.127G>T and c.487G>C, were exclusively found in PD patients, while the low-frequency variant c.537T>A was



© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License (<https://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, sharing, adaptation, distribution and reproduction in any medium or format, for any purpose, even commercially, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made.



detected both in patients and controls. Combined with bioinformatics analysis, a potentially pathogenic role of c.127G>T and c.487G>C may exert in PD risk, though no significant association was shown by statistical analysis (all $P > 0.05$).

Conclusion: Our findings suggested that the *NUS1* variants seem to not cause monogenic PD, and variants like c.127G>T and c.487G>C may, at most, exert a susceptibility to PD.

Keywords: Parkinson's disease, *NUS1*, variants, susceptibility

INTRODUCTION

Parkinson's disease (PD) is the second most prevalent progressive neurodegenerative condition after Alzheimer's disease^[1,2]. The globally pooled all-age prevalence of PD is 0.151%, which has been on the rise, especially over the past two decades, with the prevalence higher in males (0.154%) than females (0.149%), increasing with age^[3]. According to the Movement Disorder Society Clinical Diagnostic Criteria for PD (MDS-PD Criteria) in 2015, it centers on motor syndrome, including the cardinal manifestations of bradykinesia, rest tremor, and rigidity^[4]. This heterogeneous neurological disorder, which is pathologically characterized by aberrant deposition of α -synuclein and death of dopaminergic neurons in the substantia nigra, as well as nondopaminergic changes, presents various motor and non-motor symptoms^[5-7]. It is tied to a complex interplay of factors including genetics, aging, and environmental risk^[8,9], among which genetic factors are responsible for ~30% of PD cases, with 5%-10% following a monogenic inheritance pattern^[9,10-12].

Genome-wide association studies (GWAS) have provided new insights into the pathophysiology of PD, as over 90 independent significant risk variants have been revealed to be correlated with PD^[13,14], and next-generation sequencing approaches have further facilitated the identification of more PD-related gene variants^[15]. Beyond pathogenic variants in commonly implicated PD genes - such as alpha-synuclein (*SNCA*), leucine-rich repeat kinase 2 (*LRRK2*), parkin RBR E3 ubiquitin protein ligase (*PRKN*), PTEN-induced kinase 1 (*PINK1*), and parkinsonism-associated deglycase (*PARK7*, also known as *DJ-1*) - which typically exhibit with Mendelian inheritance patterns, several genetic variants with either susceptibility or protective roles have also been identified. These include variants in genes such as glucosylceramidase beta 1 (*GBA1*), microtubule-associated protein tau (*MAPT*), and DnaJ heat shock protein family (Hsp40) member C10 (*DNAJC10*), all of which are implicated in PD pathogenesis^[16-18].

The *NUS1* dehydrolipoyl diphosphate synthase subunit gene (*NUS1*) was first identified as a candidate gene for PD through trio or quad whole-exome sequencing (WES), independent case-control analysis, and *Drosophila* study^[19]. Several subsequent studies have revealed rare or low-frequency *NUS1* gene variants contributing to PD or have reported controversial conclusions^[20-25], indicating the veiled effects of the *NUS1* gene variants in PD.

In this study, we aimed to screen the *NUS1* gene variants in a PD-control cohort and evaluate the potential impacts on PD in the Han Chinese population, which may provide new insights into the *NUS1*-related genetic contribution to PD etiology.

METHODS

Study participants and clinical evaluations

A total of 512 unrelated Han Chinese sporadic PD patients (male/female: 263/249, mean age at sampling: 59.36 ± 10.92 years, mean age at onset: 55.93 ± 10.15 years) and 516 ethnically and age-matched controls (male/female: 263/253, mean age at sampling: 60.11 ± 9.76 years) without PD-related manifestations or

family history were enrolled in our cohort, of which 216 sporadic PD patients and 308 controls previously evaluated were included^[23]. According to the MDS-PD Criteria, the patients were diagnosed by two proficient neurologists. The related clinical information and peripheral blood samples were taken from all participants after obtaining written informed consent. This study was approved by the Institutional Review Board of the Third Xiangya Hospital, Central South University, Changsha, Hunan, China. All procedures followed the ethical guidelines of the Declaration of Helsinki due to human samples involved.

DNA extraction and whole-exome sequencing

Genomic DNA (gDNA) was isolated from peripheral blood using the previously reported standard phenol-chloroform extraction method^[26], and WES was fulfilled (BGI-Shenzhen, Shenzhen, China). The eligible gDNA was splintered randomly, and fragments of 200-300 bp in size were selected. The fragments were end-repaired and appended an “A” base tail at the 3’ end and adapters, followed by amplification and purification, and then enriched by hybridization with the exome array. With the non-hybridized fragments washed out, the captured fragments were amplified and sequenced on a high-throughput sequencing platform. Raw image files derived from sequencing were generated into “raw data” in FASTQ format.

Variant analysis

The raw data were filtered to obtain clean reads for subsequent bioinformatics analysis. The Burrows-Wheeler Aligner (BWA) was used to align clean reads to the human reference genome (GRCh37/hg19). Duplicate reads were marked with the Genome Analysis Toolkit (GATK) and base quality values were recalibrated with known sites, using the Single Nucleotide Polymorphism database (dbSNP) and the 1000 Genomes Project (1000G), according to the recommended GATK Best Practices. The evaluation indexes of the samples, including sequencing depth, coverage, and mapping rate, were analyzed based on the alignments. Single nucleotide polymorphisms (SNPs) and insertions/deletions (InDels) were detected by GATK HaplotypeCaller. Then, variants were annotated by tools like SnpEff or Annodb. Variant databases, including the Exome Aggregation Consortium database (ExAC, v1.0) and the Genome Aggregation Database (gnomAD, v2.1.1), were searched to determine the allele frequency of variants on a global scale. The potential PD-related variants were additionally retrieved in the Human Gene Mutation Database and PubMed to confirm whether they were previously reported^[27]. Potential disease-causing variants in the well-known monogenic PD genes, such as *SNCA*, *LRRK2*, *PRKN*, *PINK1*, *DJ-1*, and *PLA2G6* (phospholipase A2 group VI), were excluded^[27-32]. Sanger sequencing was applied to verify the screened variants using the 3730xl sequencer (Applied Biosystems, Thermo Fisher Scientific Inc., Waltham, MA, USA). According to the minor allele frequency (MAF), the detected variants were classified into three categories: rare (MAF < 0.001), low frequency (0.001 ≤ MAF ≤ 0.01), and common (MAF > 0.01).

Bioinformatics analysis

The pathogenicity of potential variants was assessed using the bioinformatics prediction tools, Combined Annotation Dependent Depletion (CADD), Polymorphism Phenotyping v2 (PolyPhen-2), Sorting Intolerant from Tolerant (SIFT), Protein Variation Effect Analyzer (PROVEAN), MutPred2, Functional Analysis through Hidden Markov Models (FATHMM), and MutationTaster2021^[18,26,33]. The protein stability changes related to substitution variants were predicted by the sequence-based Single Amino Acid Folding free Energy Changes (SAAFEC-SEQ) (<http://compbio.clemson.edu/SAAFEC-SEQ/>) and machine-learning MUPRO (<http://mupro.proteomics.ics.uci.edu/>) online tools^[34,35]. The NCBI Basic Local Alignment Search Tool (BLAST, <https://blast.ncbi.nlm.nih.gov/Blast.cgi>) was used to evaluate the sequence conservation of amino acids at variant positions among 10 species.

Statistical analysis

Pearson's chi-square test was performed to assess the gender difference in cases and controls, and an independent samples *t*-test was used to assess the age difference. Deviation from Hardy-Weinberg equilibrium was tested in controls. Pearson's chi-square test or Fisher's exact test was applied to test genotypic and allelic frequency differences between case and control groups. The statistical analysis was performed using Statistical Product and Service Solutions (version 24, SPSS Inc., Chicago, IL, USA). The *P* value < 0.05 on both sides was considered statistically significant. The gene-based analysis, optimized sequence kernel association test (SKAT-O) in R-4.4.1, was applied to analyze the obtained rare variants in both groups, with gender and age at sampling as covariates.

RESULTS

A total of three *NUS1* (NM_138459.5) heterozygous missense variants, including c.127G>T (p.Ala43Ser, rs1327892878), c.487G>C (p.Asp163His, rs369403261), and c.537T>A (p.Asp179Glu, rs28362519), were revealed by WES and confirmed by Sanger sequencing in the cohort [Figure 1A]. All three variants were detected in sporadic PD cases, with one also identified in controls. The p.Ala43Ser variant was found in two PD patients with onset age over 50 years, and the p.Asp163His variant was discovered in a 73-year-old female patient suffering from bradykinesia, rigidity, and postural instability [Table 1]. The p.Asp179Glu variant was detected in 7 PD patients and 9 controls. Two variants p.Ala43Ser and p.Asp163His with a MAF < 0.001 or absent in East Asians according to 1000G, ExAC, and gnomAD were considered rare variants, whereas p.Asp179Glu with a MAF < 0.01 was categorized as a low-frequency variant [Supplementary Table 1].

The variants, p.Ala43Ser and p.Asp163His, were predicted to be conflicting, in which over half of the pathogenicity prediction tools (4/7) predicted p.Asp163His as pathogenic, while all the tools predicted p.Asp179Glu as benign. Two missense variants, p.Ala43Ser and p.Asp163His, were predicted to reduce the protein stability by SAAFEC-SEQ or MUpro, while p.Asp179Glu was predicted to reduce the stability only by MUpro [Supplementary Table 1]. The amino acid residues, p.Ala43, p.Asp163, and p.Asp179, are highly conserved in the nine species from reptiles to mammals, except in lower organisms below zebrafish [Figure 1B].

No statistically significant difference was found in terms of gender or age between patients and controls (both *P* > 0.05). The Hardy-Weinberg equilibrium test indicated no deviation in the controls (all *P* > 0.05). Absent in controls, two potential PD-associated variants, p.Ala43Ser and p.Asp163His, had the genotype frequency of 0.39% and 0.20% in the case population, respectively. No statistically significant differences in genotypic distributions or allele frequencies between 512 PD patients and 516 controls (all *P* > 0.05) were revealed in three variants [Supplementary Table 2]. Further gene-based SKAT-O analysis showed no significant association between the identified rare variant and the PD phenotype (*P* = 0.1494 for p.Ala43Ser and *P* = 0.2893 for p.Asp163His), even combined (*P* = 0.1259 for two rare variants p.Ala43Ser and p.Asp163His, and *P* = 0.5784 for all three variants).

DISCUSSION

PD is a common complex neurodegenerative disease determined by monogenic variants or related to multiple factors^[36,37]. Since the watershed in 1997, when a pathogenic variant of the *SNCA* gene, known as the first PD-causative gene, was identified in autosomal dominant PD families^[38], a large number of genetic loci have been implicated in PD^[39]. To date, at least 26 loci and 22 genes have been definitively identified as responsible for monogenic PD^[39-41], although they account for less than 10% of cases^[42,43]. Additionally, variants in many susceptibility genes have been reported to increase the risk of PD development, recognized

Table 1. Clinical data of three PD patients with the *NUS1* c.127G>T (p.Ala43Ser) and c.487G>C (p.Asp163His) variants

Item	Case 1	Case 2	Case 3
<i>NUS1</i> variant	c.127G>T (p.Ala43Ser)	c.127G>T (p.Ala43Ser)	c.487G>C (p.Asp163His)
Gender	Male	Female	Female
Age at onset	52 years old	71 years old	70 years old
Age at sampling	54 years old	73 years old	73 years old
Family history	No	No	No
Symptoms at onset	Involuntary shaking of hands	Progressive bradykinesia and involuntary shaking of the right limb and jaw	Bradykinesia and postural deformity
Motor features			
Bradykinesia	No	Yes	Yes
Rest tremor (distribution)	Yes (two hands)	Yes (right limb)	No
Rigidity	Yes	No	Yes
Muscle tone	Increased	Increased	Increased
Muscle strength	Normal	Normal	Normal
Gait disturbance	No	Yes (festination)	Yes (festination)
Imbalance/impaired postural reflexes	No	No	Yes
Dysarthria	No	No	No
Treatment (levodopa)	375 mg/day	187.5 mg/day	562.5 mg/day
Response to levodopa	Poor	Good	Good
Levodopa-induced dyskinesia	No	No	No
Sensory abnormalities	No	No	Yes
Reflex			
Plantar response	Normal	Normal	Normal
Babinski sign	No	No	No
Cognitive decline	No	No	No
Psychiatric features	No	No	No
Sleeping dysfunction	Yes	Yes	Yes
Autonomic involvement	No	Yes (constipation)	No
Hyposmia	No	Yes	No
Others			
Cerebellar signs	No	No	No
Seizures	No	No	No
Brain magnetic resonance imaging	Scattered ischemic foci in frontal and parietal lobes	A few ischemic foci in white matter	Scattered brain ischemic foci

PD: Parkinson's disease; *NUS1*: the *NUS1* dehydrodolichyl diphosphate synthase subunit gene.

as common risk factors^[44-46]. In recent years, a research group has reported that the *NUS1* gene variants are associated with PD mainly in Chinese^[19-21]. In contrast, other studies have suggested a lack of association between the *NUS1* gene variants and PD in case-control cohorts of Chinese or European descent^[23-25].

The *NUS1* gene, located on chromosome 6q22.1, contains 5 exons and encodes the transmembrane protein, neurite outgrowth inhibitor B (Nogo-B) receptor (NgBR), which is a subunit of cis-prenyltransferase (cis-PTase)^[47-49]. The NgBR includes two types of domains, the N-terminal transmembrane domain and the cis-PTase homology domain^[50]. It is mainly distributed in the endoplasmic reticulum (ER) and the cell membrane, with a relatively high expression in nerve cells and immune cells (<http://biogps.org/>). Its stable binding to dehydrodolichyl diphosphate synthase (DHDDS) stimulates the full activity of cis-PTase, acting in dolichol synthesis and protein glycosylation in ER^[51]. The N-terminal transmembrane domains, TM1 (transmembrane domain 1) and TM3 (transmembrane domain 3), determine the orientation of the

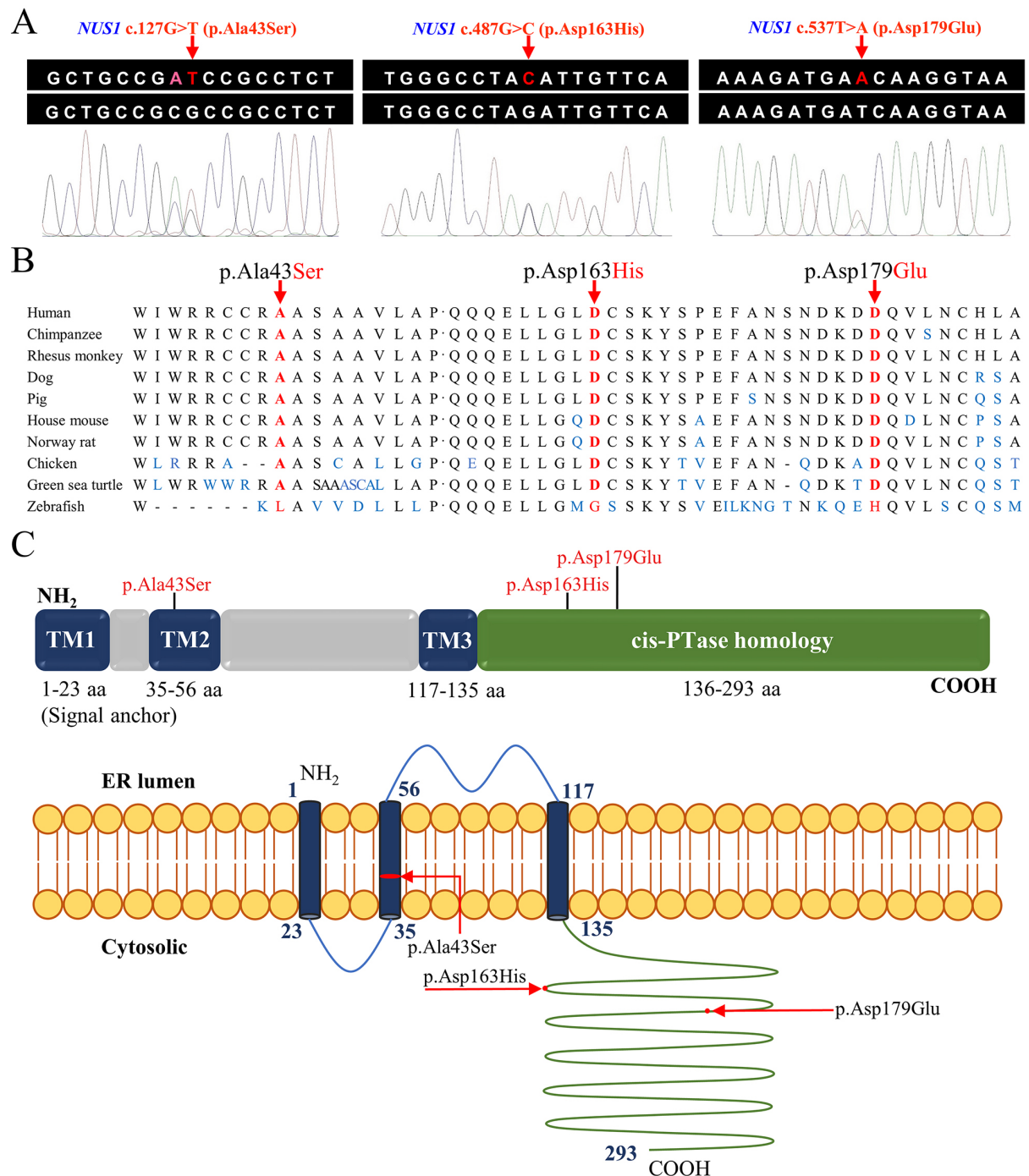


Figure 1. The three identified *NUS1* heterozygous missense variants, c.127G>T (p.Ala43Ser), c.487G>C (p.Asp163His), and c.537T>A (p.Asp179Glu). (A) The Sanger sequencing results of three missense variants, as well as a synonymous variant (c.126C>A, p.Arg42=, rs947563301) co-occurring with c.127G>T; (B) Sequence alignment of the *NUS1*-encoded NgBR protein in different species, with arrows pointing to the amino acids affected by the variants; (C) The locations of three variants in the pattern diagram and topological model of NgBR protein, mainly localized to the endoplasmic reticulum. *NUS1*: the *NUS1* dehydrolipoyl diphosphate synthase subunit gene; TM: transmembrane domain; aa: amino acid; cis-PTase homology: cis-prenyltransferase homology domain; ER: endoplasmic reticulum; NgBR, neurite outgrowth inhibitor B receptor.

C-terminal of NgBR, and the localization of the C-terminal is related to the NgBR function. When the

C-terminal is oriented toward the ER lumen, as the minor proportion, it interacts with Niemann-Pick type C2 (NPC2) protein, stabilizes the nascent NPC2, and regulates intracellular cholesterol transport^[52,53]. When the C-terminal of NgBR is oriented toward the cytosol, as the major proportion, it interacts with and stabilizes DHDDS, participating in dolichol synthesis, and affecting the protein glycosylation^[50]. The *NUS1* homozygous loss-of-function variant was identified to cause congenital disorder of glycosylation type Iaa (CDG1AA, OMIM 617082)^[54], while *de novo* heterozygous variants were shown to be associated with autosomal dominant intellectual developmental disorder-55 with seizures (MRD55, OMIM 617831)^[55]. Lower serum soluble level of Nogo-B, which may function via the Nogo-B/NgBR axis, in PD patients with poor motor function and worse disease progression, along with the observation of cholesterol accumulation and PD-related neurodegeneration features in *Drosophila* with NgBR ortholog loss, supported the potential role of *NUS1* in the pathogenesis of PD^[52,56].

In this study, we identified three *NUS1* heterozygous missense variants in our cohort, of which two variants, c.127G>T (p.Ala43Ser) and c.487G>C (p.Asp163His), were found only in patients, and c.537T>A (p.Asp179Glu) was found to have similar frequencies in PD patients and controls (7/512 vs. 9/516). The c.127G>T variant resulted in the substitution of non-polar hydrophobic alanine by polar hydrophilic serine (p.Ala43Ser). The other two variants, c.487G>C and c.537T>A, were predicted to affect amino acids in the cis-PTase homology domain, resulting in the conversion of acidic aspartic acid to basic histidine at position 163 (p.Asp163His), and the acidic residue substitution at position 179 (from aspartic acid to glutamic acid, p.Asp179Glu). The similar low frequency of p.Asp179Glu variant in our patients and controls, combined with the benign outcomes of pathogenicity predictive tools, suggested that it was not associated with PD, consistent with the findings and conclusions of previous studies^[23,24].

However, we suspected that p.Asp163His and p.Ala43Ser may pose a risk for PD in the population, which is supported by the following evidence: (i) Some *de novo* heterozygous variants in the *NUS1* gene were disease-causing variants for MRD55^[55]. (ii) To date, no co-segregated disease-causing *NUS1* variant has been found in a large family with PD^[19]. (iii) These two variants had low frequencies in the population and their bioinformatics predictions were conflicting, especially for the p.Ala43Ser variant. (iv) These two variants were identified in sporadic PD cases rather than familial cases. (v) The amino acids are highly conserved in multi-species. (vi) Particularly, the TM2 domain that the p.Ala43Ser affects may not be a determiner in the orientation of the C-terminal like TM1 and TM3 [Figure 1C]. Burden analysis of rare variants including p.Asp163His was reported to be deleterious and have an association with PD^[19-21]. Although statistical analysis showed no associations between the variants (p.Ala43Ser and p.Asp163His) and PD phenotype, combined with all the findings, we could not fully exclude a possible role in PD. Moreover, PD is a typical age-related neurological disease. These three patients were all over 50 years at age onset and had no positive family history, which suggested that the *NUS1* gene variants may play a role in increasing susceptibility in PD at most, rather than cause PD in a monogenic inheritance pattern with low penetrance.

Furthermore, even though p.Ala43Ser and p.Asp163His may potentially contribute to PD susceptibility, the *NUS1* variant(s) may affect less than 0.6% (3/512) of Han Chinese patients with PD. More studies with large-scale samples, as well as high-throughput sequencing approaches and valid bioinformatics tools, are required to verify the role of *NUS1* gene variants in PD susceptibility. In conjunction with further screening of cases with neurological disorders, including CDG1AA and MRD55, elucidating the role of the *NUS1* gene in neurological diseases, particularly neurodevelopmental conditions, will become touchable.

In summary, our study indicated that the *NUS1* gene variants seem to not cause monogenic PD, which may exert a susceptibility to PD at most. The findings enhanced the understanding of the real impact of the

NUS1 gene variants on monogenic PD by the limited samples in this study.

DECLARATIONS

Acknowledgments

The authors sincerely thank all participants and researchers for their support and cooperation in collecting DNA samples, clinical data, and genetic information.

Authors' contributions

Research conception and design: Gao C, Yuan L, Zheng W, Deng H

Data acquisition and analysis: Gao C, Yuan L, Zheng W, Yang Y, Song Z, Guo Y, Deng H

Writing & original draft: Gao C, Yuan L, Deng H

Writing & review and editing: Gao C, Yuan L, Deng H

Availability of data and materials

The data supporting the findings of this study are available within this Article and its Supplementary Information. All data obtained during the study are available from the corresponding author upon reasonable request.

Financial support and sponsorship

This work was supported by National Natural Science Foundation of China (No. 81873686), Natural Science Foundation of Hunan Province (No. 2023JJ30715), Scientific Key Research Project of Health Commission of Hunan Province (No. A202303018385), Health Research Project of Hunan Provincial Health Commission (No. W20243024), Natural Science Foundation of Changsha (No. kq2403186), Distinguished Professor of the Lotus Scholars Award Program of Hunan Province, Sublimation Scholars Project of Central South University, and Wisdom Accumulation and Talent Cultivation Project of the Third Xiangya Hospital of Central South University (No. YX202109).

Conflicts of interest

Dr. Hao Deng is an Editorial Board member of the journal *Ageing and Neurodegenerative Diseases*. Dr. Hao Deng was not involved in any steps of editorial processing, notably including reviewer selection, manuscript handling, and decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

The study involving human subjects was conducted in strict accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Third Xiangya Hospital, Central South University, Changsha, Hunan, China (No. 2018-S400). Clinical data and peripheral blood samples were collected from patients after obtaining written informed consent.

Consent for publication

Not applicable.

Copyright

© The Author(s) 2025.

REFERENCES

1. Chhetri JK, Mei S, Wang C, Chan P. New horizons in Parkinson's disease in older populations. *Age Ageing*. 2023;52:afad186. DOI PubMed
2. Deliz JR, Tanner CM, Gonzalez-Latapi P. Epidemiology of Parkinson's disease: an update. *Curr Neurol Neurosci Rep*. 2024;24:163-79. DOI PubMed

3. Zhu J, Cui Y, Zhang J, et al. Temporal trends in the prevalence of Parkinson's disease from 1980 to 2023: a systematic review and meta-analysis. *Lancet Healthy Longev.* 2024;5:e464-79. DOI PubMed
4. Postuma RB, Berg D, Stern M, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord.* 2015;30:1591-601. DOI PubMed
5. Geng L, Gao W, Saiyin H, et al. MLKL deficiency alleviates neuroinflammation and motor deficits in the α -synuclein transgenic mouse model of Parkinson's disease. *Mol Neurodegener.* 2023;18:94. DOI PubMed PMC
6. Muwanigwa MN, Modamio-Chamarro J, Antony PMA, et al. Alpha-synuclein pathology is associated with astrocyte senescence in a midbrain organoid model of familial Parkinson's disease. *Mol Cell Neurosci.* 2024;128:103919. DOI PubMed
7. González-Casacuberta I, Vilas D, Pont-Sunyer C, et al. Neuronal induction and bioenergetics characterization of human forearm adipose stem cells from Parkinson's disease patients and healthy controls. *PLoS One.* 2022;17:e0265256. DOI PubMed PMC
8. Lim SY, Klein C. Parkinson's disease is predominantly a genetic disease. *J Parkinsons Dis.* 2024;14:467-82. DOI PubMed PMC
9. Pang SY, Ho PW, Liu HF, et al. The interplay of aging, genetics and environmental factors in the pathogenesis of Parkinson's disease. *Transl Neurodegener.* 2019;8:23. DOI PubMed PMC
10. Singleton A, Hardy J. The evolution of genetics: Alzheimer's and Parkinson's diseases. *Neuron.* 2016;90:1154-63. DOI PubMed PMC
11. Cherian A, K P D, Vijayaraghavan A. Parkinson's disease - genetic cause. *Curr Opin Neurol.* 2023;36:292-301. DOI PubMed
12. Luo S, Wang D, Zhang Z. Post-translational modification and mitochondrial function in Parkinson's disease. *Front Mol Neurosci.* 2024;16:1329554. DOI PubMed PMC
13. Nalls MA, Blauwendraat C, Vallergera CL, et al; 23andMe Research Team; System Genomics of Parkinson's Disease Consortium; International Parkinson's Disease Genomics Consortium. Identification of novel risk loci, causal insights, and heritable risk for Parkinson's disease: a meta-analysis of genome-wide association studies. *Lancet Neurol.* 2019;18:1091-102. DOI PubMed PMC
14. Dulski J, Ross OA, Wszolek ZK. Genetics of Parkinson's disease: state-of-the-art and role in clinical settings. *Neurol Neurochir Pol.* 2024;58:38-46. DOI PubMed
15. Yemni EA, Monies D, Alkhairallah T, et al. Integrated analysis of whole exome sequencing and copy number evaluation in Parkinson's disease. *Sci Rep.* 2019;9:3344. DOI PubMed PMC
16. Abe T, Kuwahara T. Targeting of lysosomal pathway genes for Parkinson's disease modification: insights from cellular and animal models. *Front Neurol.* 2021;12:681369. DOI PubMed PMC
17. Benitez BA, Davis AA, Jin SC, et al. Resequencing analysis of five Mendelian genes and the top genes from genome-wide association studies in Parkinson's disease. *Mol Neurodegener.* 2016;11:29. DOI PubMed PMC
18. Yuan L, Song Z, Deng X, et al. Systematic analysis of genetic variants in Han Chinese patients with sporadic Parkinson's disease. *Sci Rep.* 2016;6:33850. DOI PubMed PMC
19. Guo JF, Zhang L, Li K, et al. Coding mutations in NUS1 contribute to Parkinson's disease. *Proc Natl Acad Sci U S A.* 2018;115:11567-72. DOI PubMed PMC
20. Jiang L, Mei JP, Zhao YW, et al. Low-frequency and rare coding variants of NUS1 contribute to susceptibility and phenotype of Parkinson's disease. *Neurobiol Aging.* 2022;110:106-12. DOI PubMed
21. Jiang L, Pan HX, Zhao YW, et al. Contribution of coding/non-coding variants in NUS1 to late-onset sporadic Parkinson's disease. *Parkinsonism Relat Disord.* 2021;84:29-34. DOI PubMed
22. Araki K, Nakamura R, Ito D, et al. NUS1 mutation in a family with epilepsy, cerebellar ataxia, and tremor. *Epilepsy Res.* 2020;164:106371. DOI PubMed
23. Yuan L, Chen X, Song Z, et al. Extended study of NUS1 gene variants in Parkinson's disease. *Front Neurol.* 2020;11:583182. DOI PubMed PMC
24. Chen X, Xiao Y, Zhou M, et al. Genetic analysis of NUS1 in Chinese patients with Parkinson's disease. *Neurobiol Aging.* 2020;86:202.e5-6. DOI PubMed
25. Bustos BI, Bandres-Ciga S, Gibbs JR, et al; International Parkinson's Disease Genomics Consortium (IPDGC). Replication assessment of NUS1 variants in Parkinson's disease. *Neurobiol Aging.* 2021;101:300.e1-3. DOI PubMed PMC
26. Li H, Yuan L, Yang H, et al. Analysis of SOD1 variants in Chinese patients with familial amyotrophic lateral sclerosis. *QJM.* 2023;116:365-74. DOI PubMed
27. Deng X, Zheng W, Yang Y, et al. Identification of PLA2G6 variants in a Chinese patient with Parkinson's disease. *Ageing Neur Dis.* 2023;3:9. DOI
28. Guo Y, Sun Y, Song Z, et al. Genetic analysis and literature review of SNCA variants in Parkinson's disease. *Front Aging Neurosci.* 2021;13:648151. DOI PubMed PMC
29. Fan K, Hu P, Song C, et al. Novel compound heterozygous PRKN variants in a Han-Chinese family with early-onset Parkinson's disease. *Parkinsons Dis.* 2019;2019:9024894. DOI PubMed PMC
30. Wang P, Guo Y, Song C, Liu Y, Deng H. PINK1 p.K520RfsX3 mutation identified in a Chinese family with early-onset Parkinson's disease. *Neurosci Lett.* 2018;676:98-102. DOI PubMed
31. Skou LD, Johansen SK, Okarmus J, Meyer M. Pathogenesis of DJ-1/PARK7-mediated Parkinson's disease. *Cells.* 2024;13:296. DOI PubMed PMC
32. Tezuka T, Ishiguro M, Taniguchi D, et al. Clinical characteristics and pathophysiological properties of newly discovered LRRK2 variants associated with Parkinson's disease. *Neurobiol Dis.* 2024;199:106571. DOI PubMed

33. Pejaver V, Urresti J, Lugo-Martinez J, et al. Inferring the molecular and phenotypic impact of amino acid variants with MutPred2. *Nat Commun.* 2020;11:5918. [DOI](#) [PubMed](#) [PMC](#)
34. Li G, Panday SK, Alexov E. SAAFEC-SEQ: a sequence-based method for predicting the effect of single point mutations on protein thermodynamic stability. *Int J Mol Sci.* 2021;22:606. [DOI](#) [PubMed](#) [PMC](#)
35. Cheng J, Randall A, Baldi P. Prediction of protein stability changes for single-site mutations using support vector machines. *Proteins.* 2006;62:1125-32. [DOI](#) [PubMed](#)
36. Yao LY, Guo JF, Wang L, et al. LRRK2 Pro755Leu variant in ethnic Chinese population with Parkinson's disease. *Neurosci Lett.* 2011;495:35-8. [DOI](#) [PubMed](#)
37. Imbriani P, Martella G, Bonsi P, Pisani A. Oxidative stress and synaptic dysfunction in rodent models of Parkinson's disease. *Neurobiol Dis.* 2022;173:105851. [DOI](#) [PubMed](#)
38. Polymeropoulos MH, Lavedan C, Leroy E, et al. Mutation in the alpha-synuclein gene identified in families with Parkinson's disease. *Science.* 1997;276:2045-7. [DOI](#) [PubMed](#)
39. Deng H, Wang P, Jankovic J. The genetics of Parkinson disease. *Ageing Res Rev.* 2018;42:72-85. [DOI](#) [PubMed](#)
40. Deng X, Yuan L, Jankovic J, Deng H. The role of the PLA2G6 gene in neurodegenerative diseases. *Ageing Res Rev.* 2023;89:101957. [DOI](#) [PubMed](#)
41. Andrews SV, Kukkle PL, Menon R, et al; Parkinson Research Alliance of India (PRAI). The genetic drivers of juvenile, young, and early-onset Parkinson's disease in India. *Mov Disord.* 2024;39:339-49. [DOI](#) [PubMed](#)
42. Vollstedt EJ, Madoev H, Aasly A, et al. Establishing an online resource to facilitate global collaboration and inclusion of underrepresented populations: experience from the MJFF Global Genetic Parkinson's Disease Project. *PLoS One.* 2023;18:e0292180. [DOI](#) [PubMed](#) [PMC](#)
43. Navarro E, Esteras N. A new mutation in the Parkinson's-related FBOXO7 gene impairs mitochondrial and proteasomal function. *FEBS J.* 2024;291:2562-4. [DOI](#) [PubMed](#)
44. Shadkam R, Saadat P, Azadmehr A, Chehrizi M, Daraei A. Key non-coding variants in three neuroapoptosis and neuroinflammation-related lncRNAs are protectively associated with susceptibility to Parkinson's disease and some of its clinical features. *Mol Neurobiol.* 2024;61:2854-65. [DOI](#) [PubMed](#)
45. Huang X, Zhao Y, Pan H, et al. The association between LIN28A gene rare variants and Parkinson's disease in Chinese population. *Gene.* 2022;829:146515. [DOI](#) [PubMed](#)
46. Yu M, Ye H, De-Paula RB, et al. Functional screening of lysosomal storage disorder genes identifies modifiers of alpha-synuclein neurotoxicity. *PLoS Genet.* 2023;19:e1010760. [DOI](#) [PubMed](#) [PMC](#)
47. Long SL, Li YK, Xie YJ, Long ZF, Shi JF, Mo ZC. Neurite outgrowth inhibitor B receptor: a versatile receptor with multiple functions and actions. *DNA Cell Biol.* 2017;36:1142-50. [DOI](#) [PubMed](#)
48. Fliesler SJ, Ramachandra Rao S, Nguyen MN, KhalafAllah MT, Pittler SJ. Vertebrate animal models of RP59: current status and future prospects. *Int J Mol Sci.* 2022;23:13324. [DOI](#) [PubMed](#) [PMC](#)
49. Edani BH, Grabińska KA, Zhang R, et al. Structural elucidation of the cis-prenyltransferase NgBR/DHDDS complex reveals insights in regulation of protein glycosylation. *Proc Natl Acad Sci U S A.* 2020;117:20794-802. [DOI](#) [PubMed](#) [PMC](#)
50. Harrison KD, Park EJ, Gao N, et al. Nogo-B receptor is necessary for cellular dolichol biosynthesis and protein N-glycosylation. *EMBO J.* 2011;30:2490-500. [DOI](#) [PubMed](#) [PMC](#)
51. Williams LJ, Waller S, Qiu J, et al. DHDDS and NUS1: a converging pathway and common phenotype. *Mov Disord Clin Pract.* 2024;11:76-85. [DOI](#) [PubMed](#) [PMC](#)
52. Xue J, Zhu Y, Wei L, et al. Loss of Drosophila NUS1 results in cholesterol accumulation and Parkinson's disease-related neurodegeneration. *FASEB J.* 2022;36:e22411. [DOI](#) [PubMed](#)
53. Harrison KD, Miao RQ, Fernandez-Hernández C, Suárez Y, Dávalos A, Sessa WC. Nogo-B receptor stabilizes Niemann-Pick type C2 protein and regulates intracellular cholesterol trafficking. *Cell Metab.* 2009;10:208-18. [DOI](#) [PubMed](#) [PMC](#)
54. Park EJ, Grabińska KA, Guan Z, et al. Mutation of Nogo-B receptor, a subunit of cis-prenyltransferase, causes a congenital disorder of glycosylation. *Cell Metab.* 2014;20:448-57. [DOI](#) [PubMed](#) [PMC](#)
55. Hamdan FF, Myers CT, Cossette P, et al; Deciphering Developmental Disorders Study. High rate of recurrent de novo mutations in developmental and epileptic encephalopathies. *Am J Hum Genet.* 2017;101:664-85. [DOI](#) [PubMed](#) [PMC](#)
56. Liang H, Guo W, He H, et al. Decreased soluble Nogo-B in serum as a promising biomarker for Parkinson's disease. *Front Neurosci.* 2022;16:894454. [DOI](#) [PubMed](#) [PMC](#)